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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,688	10/28/2003	Jeroen Mattijs Bezemer	05032-00044	3925

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EXAMINER	
BERKO, RETFORD O	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,688	BEZEMER ET AL.	
	Examiner	Art Unit	
	Retford Berko	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections-35 USC Sec 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the independent claim 1 which describes the process of making the polymer loaded with bioactive agents, given the broadest interpretation, includes all polymers but the specification provides support for only one type of copolymer (i.e. poly(ethylene glycol)terephthalate/poly(butylenes terephthalate; abbreviated as PEG/PBT)). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with the claim.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C., first paragraph, have been described in In re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (a) the nature of the invention; (b) the state of the prior art; (c) the relative skill of those in the art; (d) the predictability of the art; (e) the breadth

of the claims; (f) the amount of direction or guidance presented (g) the presence or absence of working examples; and (h) the quantity of experimentation necessary.

(a) the nature of the invention: the claims are drawn toward a process for preparing polymer loaded with one or more bioactive agents or drugs for delivery to tissues.

(b) the state of the prior art: the state of the art in preparing polymers carrying drugs is well defined in the art and the process in the instant claims are considered conventional.

(c) the relative skill of those in the art: the relative skill of those practicing the art making drug delivery agents and devices carrying drugs wherein the agents or devices are made of polymers is not high in that any person with minimum education can make polymeric drug delivery agents and incorporate drugs in said agents.

(d) the predictability of the art: the examiner takes the position that it is highly likely that one can successfully make drug delivery agents by mixing a polymer solution with a solution of drug or bioactive agent dissolved in appropriate solvent.

(e) the breadth of the claim: the claim for the process for preparing a polymer loaded with bioactive agents, given the broadest interpretation, contemplates the use of all polymers, either homopolymers or copolymers of any size or length. However, as discussed above, only one working example is disclosed in the specification in which the PEGT/PBT copolymer is used. Therefore contrary to the claims, applicant process of making polymer loaded with bioactive agents is enabled only when PEGT/PBT polymer forms the matrix. In short, the claims are overbroad and the specification does not support the breadth of the claims.

(f) the amount of direction or guidance presented: In the specification (e.g. pages 3-5) applicant has disclosed suitable examples of polymers to be loaded with one or more bioactive agents.

Applicant also has disclosed polymers comprising of hydrophilic and hydrophobic blocks. As only one example of a polymer comprising of hydrophobic block is disclosed (see spec. at page 3, lin 25-30).

(g) the presence or absence of working examples: this is discussed above.

(h) the quantity of experimentation necessary: given the state of the art in making drug delivery agents or devices made of polymers, a person skilled in the art would be burdened with undue "painstaking experimentation study in order to determine the suitability of all types of polymers for use in the process. Therefore applicant is advised to narrow the scope of independent claims.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(i) Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "allowing the first solvent to migrate into the second solvent to obtain a solid, fibrous polymer loaded with bioactive agent; i.e. step (d)" in claim 1.

There is insufficient antecedent basis for this limitation in the claim because the first solvent in step (a) of the process is already consumed when it is mixed with the bioactive agent solution, referring back to the first solution makes the steps indefinite.

Applicant may overcome the indefiniteness in the claim by specifying what is the source of the oil and then eliminating the reference to the first solvent as this is consumed in the step (b).

(ii) Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, applicant recites a "process for preparing a polymer loaded with one or more bioactive agents comprising specified steps (a)-(d). Step (a) refers to a first solvent; said solvent is the polymer solution. In step (b), applicant adds aqueous solution of the bioactive agent to the polymer solution (i.e. first solution) to obtain a water-oil emulsion. This is indefinite and the issue is the indefinite source of the oil—i.e. is the oil in the first solution or it is in the bioactive agent solution?

Applicant may overcome the indefiniteness in the claim by specifying the source of the oil; i.e. the w/o emulsion is formed because there is oil in the first solvent (step a) or there is oil in the solution at step (b).

(iii) Claims 15 and 16 provides for the use of bioactive agent loaded polymer as a carrier for controlled release or scaffold for tissue engineering, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 15 and 16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*,

255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). Therefore, claims 15 and 16 are not reviewed as they are use claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. under 35 U.S.C. 103(a) as being unpatentable over McGinity et al (US 5, 288, 502) in view of Subramaniam et al (US 5, 874, 029) further in view of Goedemoed et al (US 5, 980, 948)

The claims are drawn to a process of preparing a polymer loaded with one or more bioactive agents. According to the claims, a polymer solution is prepares; said solution is added to an aqueous solution of a drug yielding a water-oil emulsion (w/o emulsion); immersing the w/o emulsion in a second solvent by injecting the w/o emulsion through a nozzle and allowing the solvent to migrate into the polymer solution. The claims are also directed toward the process wherein the polymer is biocompatible and biodegradable; that the polymer comprises of amphiphilic copolymer, comprising of hydrophilic blocks and hydrophobic blocks; that the polymer is a copolymer of polyakylene glycol and aromatic ester and the compounds or bioactive agents are drugs such as antitumor agents, immunogenic agents growth factors and anti-fungal agents.

McGinity et al (Patent '502), similar to applicant's claims 1, 2, 3 and 5-14; disclose methods for preparing w/o emulsions and multi-phase microspheres wherein the polymers are

used for preparing the microspheres (col 30, lin 51-60); said microspheres possess efficient drug loading and serve as drug delivery systems and wherein many compounds such as proteins, peptides and drugs are encapsulated (abstract, col 8, lin 26-34; col 16, lin 10-20; col 32, lin 50-65). According to McGitty, the steps involve the use of a nozzle; i.e. the w/o emulsion is poured through said nozzle into a second mineral oil to form a w/o/o multiple emulsion (col 16, lin 10-20 and col 17, lin 10-15) and the use of biodegradable polymers as matrices (col 30, lin 35-60) and the use of compounds of therapeutic value (col 28, lin 25-40; col 32, lin 55-65).

Patent '502 does not disclose: (i) the use of a second solvent (i.e. the w/o emulsion is not passed through a nozzle into a second solvent) and (ii) the use of copolymers made of hydrophilic blocs and hydrophobic blocs wherein the copolymers of polyalkylene and aromatic esters (e.g. poly(ethylene glycol)terephthalate/poly(butylenes terephthalate; abbreviated as PEG/PBT).

Subramaniam et al (Patent '029) disclose the use of a second solvent. Patent '029 discloses a method and apparatus for the production of submicron particles wherein pharmaceutical agents can be mixed with a solvent and the mixture is passed through a nozzle to produce a spray of atomized droplets. Patent '029 discloses the rates of atomization, mass transfer rates and the procedural steps involved (col 5, lin 35 to lin 65 continuing to col lin 1 to 15). Patent '029 discloses the solvents used for dissolving the steroid –dimethylsulfoxide (col 7, lin 10 the average size of the particles (col 7, lin 60), pressure control, the gas used for atomization (col 9, lin 65), the mean droplet diameter (col 10, lin 35). Patent '029 discloses atomization rates and mass transfer rates, suggesting that an uptimum mass transfer rate exists for production of sub-micron particles (col 5, lin 45-50); discloses the use of antisolvent (col 6,

lin 20-50 and col 15, lin 15-45) wherein the solvent and antisolvent mix in a chamber within the unit apparatus (col 8, lin 25-30). Patent '029 discloses that the nozzle in the apparatus can be used in a wide range of operating conditions in order to substantially reduce particle size and to increase surface area (col 10, lin 45-50). Patent '029 discloses the use of supercritical fluid (col 6, lin 45-50) and conditions (col 9, lin 25, 50-55 and col 10, lin 50-60).

Patent '029 does not disclose the use of copolymers made of hydrophilic blocs and hydrophobic blocs wherein the copolymers of polyalkylene and aromatic esters (e.g. poly(ethylene glycol)terephthalate/poly(butylenes terephthalate; abbreviated as PEG/PBT)

As in instant claims 3 and 4, Goedemoed et al (Patent '948) disclose the use of PEG/PBT copolymers as drug delivery matrices (col 1, lin 55-65; col 3, lin 30-35; col 11, lin 60 and col 40, lin 15-40). According to the disclosure in Goedemoed et al, the a biologically active agent may be contained in the polyester matrix formed by the PEGT/PBT matrix (col 3, lin 40-45). Patent '948 discloses that PEGT/PBT copolymer is formed into microspheres which contain biologically active agent (a wide spectrum of agents is disclosed; col 4-8) such as drug or protein and that the polyester copolymer protects the biologically active agents by preventing denaturation of the biologically active agent until the biologically active agent reaches the desired cell, tissue or organ (col 14, lin 10-15).

One of ordinary skill in the art would be motivated to devise a method for making drug delivery devices using PEGT/PBT matrices wherein the steps involve formation of w/o emulsions (Patent '948; col 12, lin 55-60) in combination with the use of a second solvent as in the cited prior art (Patent '029). One of ordinary skill would expect reasonable success in forming PEGT/PBT microspheres for delivery of drugs, immunogenic proteins and other

biologically active agents that are susceptible to denaturation. The motivation to combine the references cited lies in the advantage provided by the ability of the matrices used to protect the labile biologically active agents from denaturation by polyester PEGT/PBT copolymer. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Retford Berko** whose telephone number is 703-305-4442. The examiner can normally be reached on M-F from 8.00 am to 5.30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Thurman K Page**, can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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